CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203479Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS NDA REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-479	**Reviewer:** Deepika Arora Lakhani, PhD	
Submission Date:	22-AUG-2012 20-JULY-2012 24-MAY-2012 29-DEC-2011		
Division:	Division of Psychiatry Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	Douglas Pharmaceuticals America	**Biopharmaceutics Supervisor (Acting):** Richard Lostritto, PhD	
Trade Name:	(b) (4)™ (Proposed)	**Date Assigned:**	Jan 25, 2012
Generic Name:	CLOZAPINE USP	**Date of Review:**	Aug 27, 2012
Indication:	Management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment of schizophrenia	**Type of Submission:** New Drug Application 505b(2)	
Formulation/ strengths	Oral Suspension, 50 mg/mL		
Route of Administration	Oral		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

The NDA submission is a 505(b)(2) application for Clozapine Oral Suspension, 50 mg/mL, relying on the previous finding of safety and efficacy of the listed drug Clozaril® (Clozapine Tablets), NDA 19-758. The 505(b)(2) NDA provides for a change in dosage form (i.e., from an oral tablet to an oral suspension), as well as for a change in strength (from 100 mg to 50 mg). Clozapine is approved for the management of treatment resistant schizophrenia and to reduce the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder. There are currently no liquid /suspension dosage forms of clozapine in the U.S.

Clozapine Oral Suspension, 50 mg/mL is a free-flowing, yellow suspension, with a density of about (b) (4) g/mL. This review focuses on evaluating the acceptability of the proposed dissolution method and acceptance criteria.

Dissolution Method and Acceptance Criteria:

The following method to assay the dissolution of clozapine oral suspension was developed. The following acceptance criterion was recommended by the Agency and accepted by the Applicant on 22-AUG-2012.

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criterion
Clozapine	Suspension	II (paddle)	50	pH 4.0 Acetate Buffer	900 mL	Q= (b) (4) % at 15 minutes

The robustness of the dissolution method was evaluated by assessing the effect of changing dissolution parameters (paddle speed). The discriminating capacity of the dissolution method was evaluated by varying the amount of (b) (4) in the formulation. The proposed dissolution method discriminates for (b) (4) concentration and has been deemed acceptable.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 203-479 and its amendments submitted on 24-MAY-2012, 20-JULY-2012, 22-AUG-2012 and 28-DEC-2012. The following dissolution method for clozapine oral suspension is deemed acceptable:

USP Apparatus II
Paddle speed: 50 rpm
Volume/Temp: 900 ml / 37°C
Medium: pH 4.0 Acetate Buffer ;

The following dissolution acceptance criterion has been recommended (and agreed by the Applicant, refer to submission dated 22-AUG-2012) for clozapine oral suspension.

Q= (b) (4) % at 15 minutes

From the Biopharmaceutics perspective NDA 203-479 for (b) (4) (clozapine) Oral Suspension is recommended for APPROVAL.

Deepika Arora Lakhani, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, PhD
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. *on file; RLostritto*

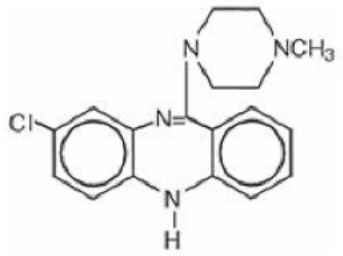
BIOPHARMACEUTICS ASSESSMENT

INTRODUCTION

Clozapine is approved for the management of treatment resistant schizophrenia and to reduce the risk of recurrent suicidal behavior in patients with schizophrenia and schizoaffective disorder. There are currently no liquid /suspension dosage forms of clozapine in the U.S. This NDA submission is a 505(b)(2) application for Clozapine Oral Suspension, 50 mg/mL, relying on the previous finding of safety and efficacy of the listed drug Clozaril® (Clozapine Tablets), NDA 19-758. The proposed product, Clozapine Oral Suspension, 50 mg/mL is a free-flowing, yellow suspension, with a density of about (b) (4) g/mL.

Drug Substance

Clozapine is almost insoluble in water and soluble in dichloromethane, ethanol, and methanol.



$C_{18}H_{19}ClN_4$ Mol. Wt. 326.83

Figure 1. Chemical Structure of Clozapine

Drug Product

The Drug Product contains 50 mg/mL and is free-flowing suspension with a density of (b) (4) g/mL. The quantitative composition of the suspension is provided in Table 1.

Table 1. Quantitative Composition of Drug Product

Component	Grade	w/w%	Qty/Unit (mg/mL)	Commercial Batch Size (b) (4) Kg (b) (4) L) (kg)	Pharmaceutical Function	IID Limits[3] (oral route of administration)
Clozapine	USP	(b) (4) %	50.00	(b) (4)	Active	N/A
Sorbitol (b) (4)	USP	(b) (4)				(b) (4)
Povidone (b) (4)	USP					
Sodium Dihydrogen Phosphate Dihydrate	USP					

Sodium Hydroxide	NF	(b) (4)	(b) (4)
(b) (4)	NF		
Methylparaben sodium	NF		
Propylparaben sodium	NF		
Xanthan gum	NF		
Glycerin	USP		
Water	USP		N/A
Total	-		--

[1] May be adjusted between (b) (4)
[2] May be adjusted between
[3]Information provided from FDA's Inactive Ingredient Database, last updated Oct 14, 2011.
[4] Information provided from FDA's Inactive Ingredient Database update of Oct 22, 2010.

Formulation Development

The critical aspects of suspension formulation which were targeted were:

1. Ensuring chemical stability of the active by controlling pH
2. Formation of a suitably flocculated system
3. Inhibiting clozapine crystal growth

The physicochemical properties of Clozapine Suspension relevant to product performance were determined to be pH, particle size, rheological properties, redispersibility and (b) (4), and dissolution of clozapine. Following extended periods of storage, Clozapine has been observed to settle, which if left unchecked could compromise dosing accuracy. The redispersability studies demonstrated that the suspension should be shaken for a period of at least 10 seconds or until the clozapine is visually redispersed.

Clozapine Oral Suspension is manufactured using (b) (4)

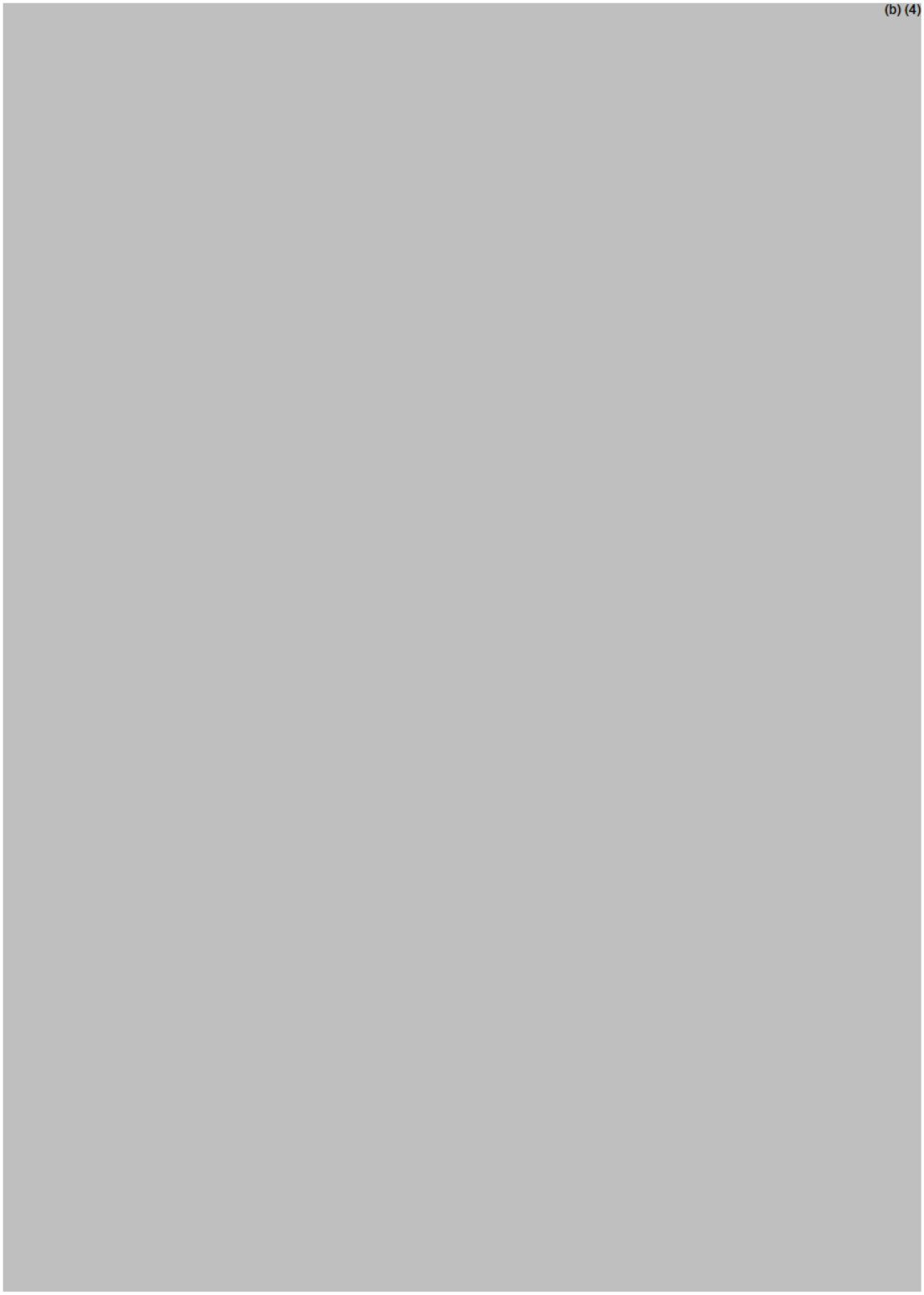
A brief overview of the manufacture of the drug product is summarized in the diagram below.

(b) (4)™ Oral Suspension

Douglas Pharmaceutical America

High-level Manufacturing Process Flow Diagram

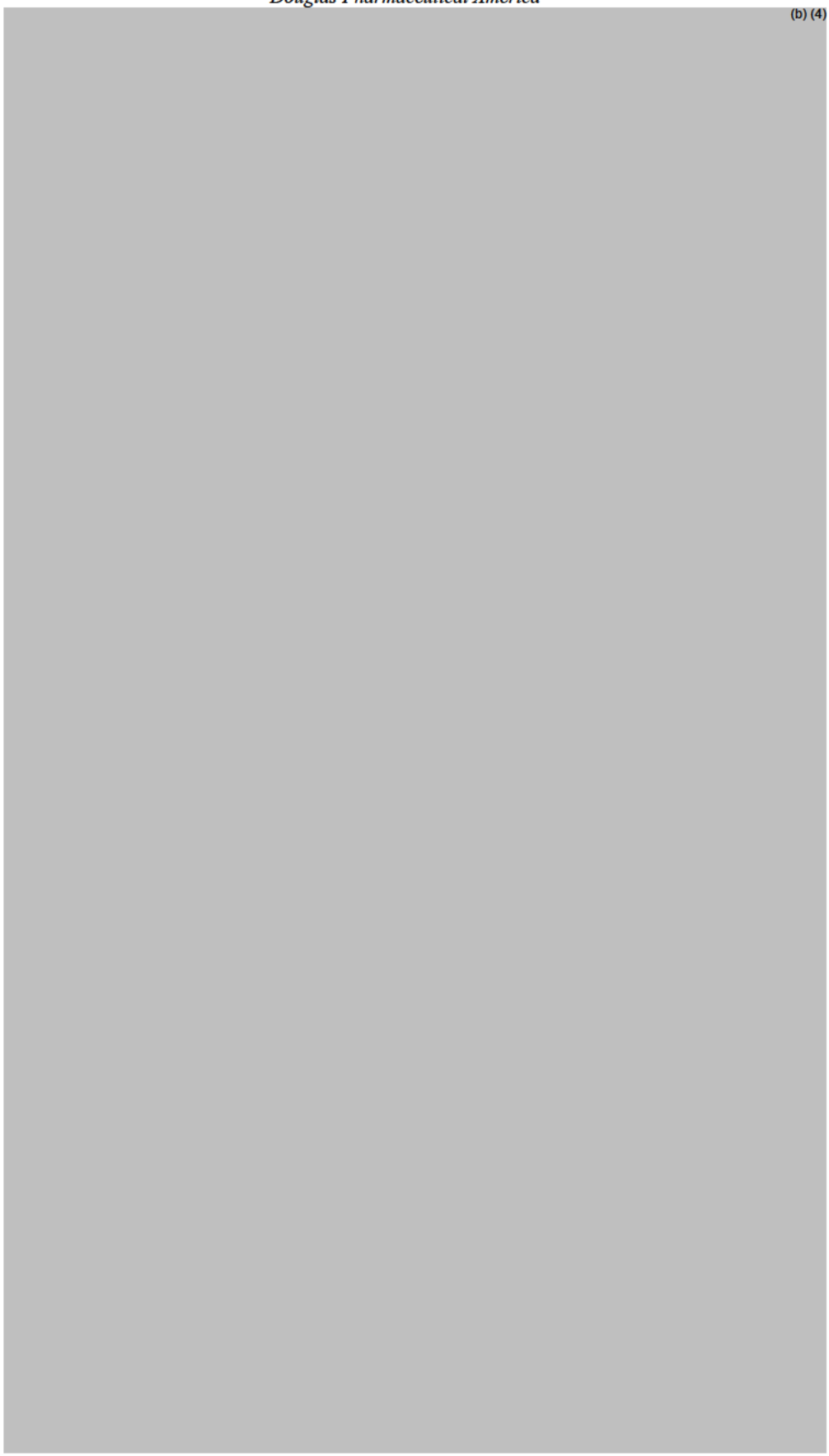
(b) (4)



(b) (4)™ Oral Suspension

Douglas Pharmaceutical America

(b) (4)



DISSOLUTION METHOD

The dissolution method that is being proposed as a quality control tool for (b) (4) (clozapine) oral suspension is summarized below:

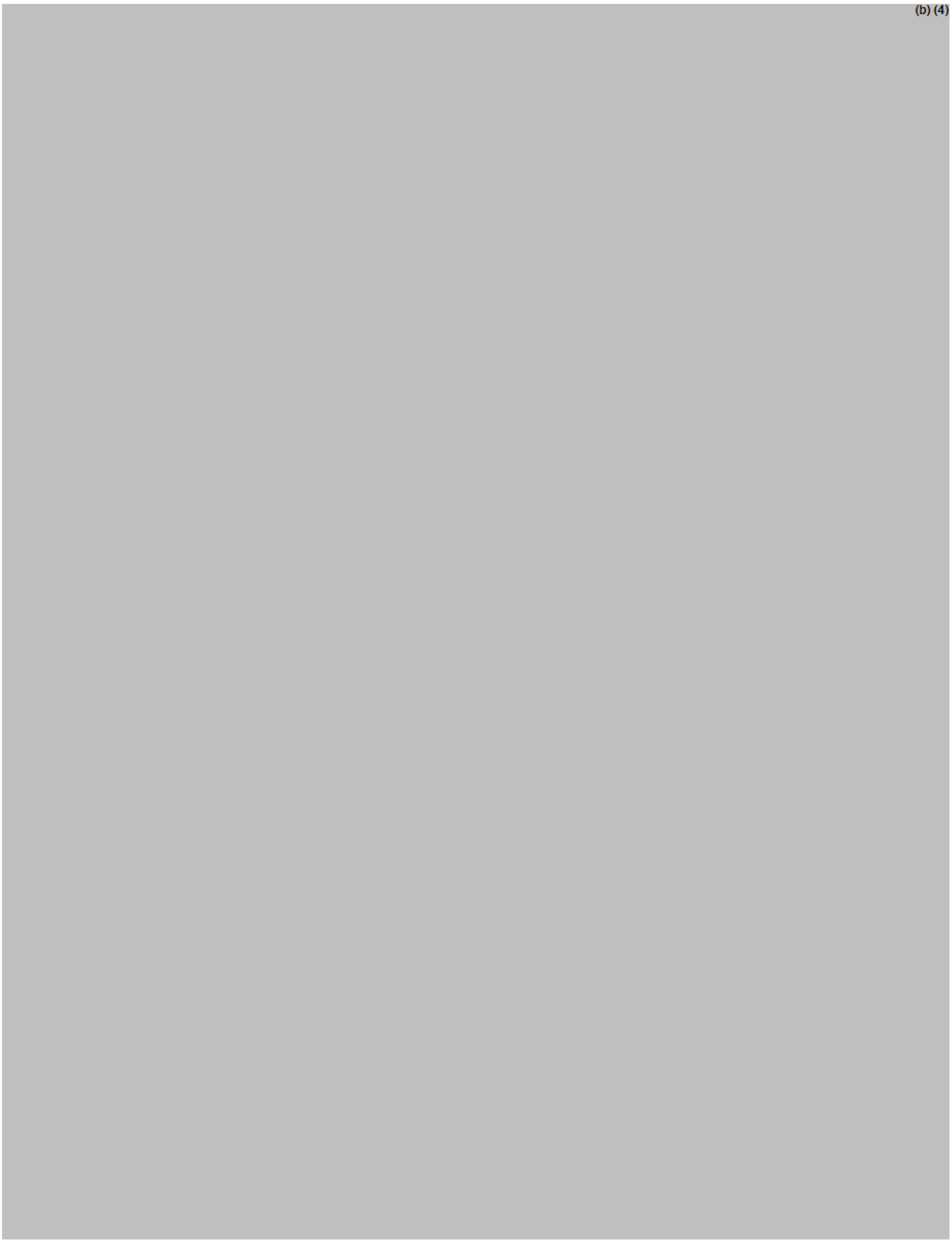
Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criterion
Clozapine	Suspension	II (paddle)	50	pH 4.0 Acetate Buffer	900 mL	Q= (b) (4) % at 15 minutes

DISSOLUTION METHOD DEVELOPMENT

Apparatus Conditions

(b) (4)

(b) (4)



(b) (4)

[redacted]

(b) (4)

(b) (4)

(b) (4)

[redacted]

DISSOLUTION ACCEPTANCE CRITERIA

The following dissolution acceptance criterion was originally proposed by the Applicant as a QC for the release of clozapine oral suspension:

(b) (4)

[redacted]

(b) (4)

[redacted]

Reviewer's Recommended Dissolution Acceptance Criteria

The following dissolution acceptance criterion is recommended as a QC for release and on stability for clozapine oral suspension:

Dissolution Acceptance Criteria
Q= (b) (4) % at 15 mins

The dissolution acceptance criteria of Q= (b) (4) % in 15 min for clozapine suspension was established based on the provided batch release data and mean dissolution data. It must be noted that only one batch at one testing point showed a slower release of (b) (4) % (Batch 7805.005A and will pass at S2). Besides the one observation, all batches support the reviewer's recommended acceptance criterion.

CONCLUSIONS

NDA 203-479 is recommended for Approval from a Biopharmaceutics perspective. The following dissolution method and acceptance criterion for the clozapine oral suspension are acceptable:

USP Apparatus	Speed (rpm)	Volume (ml) & Temperature	Medium	Acceptance Criterion
II (paddle)	50	900 mL 37°C	pH 4.0 Acetate Buffer	Q=(b) (4)% at 15 minutes

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEEPIKA LAKHANI
09/04/2012
Recommend Approval from Biopharmaceutics perspective.

ANGELICA DORANTES
09/04/2012

Clinical Pharmacology Review

PRODUCT (Generic Name):	Clozapine Suspension
PRODUCT (Brand Name):	Clozaril
DOSAGE FORM:	Suspension
INDICATION:	Treatment Resistant Schizophrenia
DOSAGE STRENGTHS:	50 mg/ml
NDA:	203479
SUBMISSION DATE:	January 6, 2012
SPONSOR:	Douglas Pharmaceuticals America
REVIEWER	Andre Jackson

REVIEW OF BE STUDY

1. EXECUTIVE SUMMARY

The NDA for clozapine oral suspension was filed as a 505(b)(2) whose approval will be based upon being bioequivalent to the reference listed drug, Clozaril ® tablets.

We found that the 50 mg/ml clozapine suspension is bioequivalent (BE) to Clozaril ® tablets. Food effect following administration of clozapine suspension is similar to Clozaril ® tablets. The sponsor has conducted a multiple dose two-treatment, two-period, two-sequence crossover bioequivalence study, performed under fasting and fed conditions and at steady state. The study compared the 50 mg/ml suspension to the Clozaril® 100 mg reference tablets. Study results indicated that under both fed and fasted conditions, the 90% confidence intervals for Log_{10} AUC(0-tau) and Log_{10} Cmax were within the acceptable limits of 80-125% of the reference.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of clozapine oral suspension. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	Yes	Pending labeling
Pivotal BE	Yes	
Food Effect	Yes	
Labeling	No	Pending satisfactory agreement with sponsor

1.2 Labeling Recommendations:

The office clinical pharmacology recommends the following changes in the proposed label:

12.3 Pharmacokinetics

Absorption

In man, clozapine tablets (25 and 100 mg) are equally bioavailable relative to a clozapine solution. (b) (4) (clozapine, USP) Oral Suspension is bioequivalent to Clozaril® (clozapine) tablets. Following dosing of multiples of 100 mg (b) (4) (clozapine, USP), once daily, the average steady-state peak plasma concentration was 275 ng/mL (range: 105 - 723 ng/mL), occurring at the average of 2.2 hours (range: 1-3.5 hours) after dosing. The average minimum concentration at steady state was 75 ng/mL (range: 11-198 ng/mL).

When (b) (4) (clozapine, USP) was administered after a high fat meal there was no effect on the AUCss or Cminss, however Cmax was reduced about 20% and there was a slight delay in Tmax of 0.5 hr from a median Tmax of 2.0 hours under fasted conditions to 2.5 hours under fed conditions. Therefore (b) (4) (clozapine, USP) may be taken without regard to meals.

2. QUESTIONS BASED REVIEW

2.1 Was the 50 mg/ml clozapine suspension BE to the 100 mg Clozaril tablet at steady-state under fasting conditions?

Yes. The 90% confidence intervals for AUC 0-tau and Cmax indicated that the 50 mg/ml suspension was BE to the 100 mg Clozaril tablet under fasting conditions at steady-state (Table 1).

Table 1. Results for comparison of suspension and Clozaril tablet under fasting conditions at steady-state.

Fasting				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
$AUC_{0\text{-}tau}$ (ng.h/ml)	2930.94	3039.18	96.44	0.924, 1.007
AUC_{∞}	Not applicable to multidose study at steady state			
C_{max} (ng/ml)	260.07	261.34	99.51	0.946, 1.047
C_{min} (ng/ml)	65.16	64.39	101.20	0.978, 1.047

2.2 Is the food effect similar between the 50 mg/ml clozapine suspension and Clozaril 100 mg tablet?
Yes. The 90% confidence intervals for AUC 0-tau and Cmax indicated that the 50 mg/ml suspension met BE criteria to the 100 mg Clozaril tablet under fed conditions at steady-state (Table 2).

Table 2. Results for comparison of suspension and Clozaril tablet under fed conditions at steady-state.

Fed				
$AUC_{0\text{-}tau}$	2806.77	2878.83	97.50	0.934, 1.018
AUC_{∞}	Not applicable to multidose study at steady state			
C_{max}	206.46	209.63	98.49	0.937, 1.035
C_{min}	63.10	62.22	101.40	0.988, 1.041

3. Division of Bioequivalence and GLP Compliance Office of Scientific Investigations Report

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 27, 2012

TO: Thomas P. Laughren M.D.
Director,
Division of Psychiatry Products

FROM: Arindam Dasgupta Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, R.Ph., Ph.D.
Chief, Bioequivalence Branch,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

and

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 203-479, Clozapine oral suspension, 50 mg/ml sponsored by Douglas Pharmaceuticals America Ltd.

At the request of the Division of Psychiatry Products (DPP), the Division of Bioequivalence and GLP Compliance (DBGLPC), conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: C11-005-LBB (ZPS 411)
Study Title: Multiple-dose, multi-centre, randomized, bioequivalence study of clozapine in multiples of
100 mg using 50 mg/ml Clozapine suspension (Douglas, America) in a two way crossover comparison with multiples of 100 mg using Clozaril 100 mg tablet (Novartis, USA) in stable patients under fasting and fed conditions and at steady state.

BACKGROUND:

This study enrolled 30 subjects, males and non-pregnant females (18-55 yrs), who were receiving treatment with multiple doses of 100 mg clozapine once daily, and stabilized (for at least 3 months after enrollment and randomization)for psychotic illnesses, but were otherwise in good health. There were no dropouts and all 30 subjects completed the study. Seventeen subjects were enrolled at the clinical site in Dunedin, New Zealand, and 13 subjects were enrolled at the clinical site in Hamilton, New Zealand.

OBJECTIVE:

The primary objectives of the study were to compare the bioavailability and bioequivalence of clozapine Test (Clozapine suspension, 50 mg/mL) and Reference (Clozaril® 100 mg tablets) formulations in stabilized adult patients under fasting and fed conditions. The secondary objectives were to assess the overall safety of the patients with regard to adverse events and standard laboratory evaluations.

The inspections were conducted by ORA Investigator Craig Garmendia (CG) and DBGLPC Scientist Arindam Dasgupta (AD). The inspection of the clinical site#1 and analytical Site#1 were conducted at Zenith Technology Corporation Ltd., Dunedin, New Zealand (By CG and AD). The inspection of the clinical site #2 was conducted at Waikato Hospital, Hamilton, New Zealand (by CG). The audits included a thorough review of study records, examination of facilities, equipment, and interviews and discussions with the firms' management and staff.

Following the inspection of the clinical and analytical sites, a Form FDA 483 was issued at each site (**Attachment 1-3**). Response to the inspectional observations from clinical sites 1 and 2 were received on June 7 and June 10, 2012, respectively (**Attachments 4-5**). A response to the inspectional observations from the analytical site was received on June 15, 2012(**Attachment 6**). DBGLPC's evaluation of the inspectional observations and the firm's responses follows:

Clinical site 1:
Zenith Technology Corporation Ltd., Dunedin, New Zealand (Inspection Dates: May 14-22, 2012 by CG and AD, Response to FDA-483: June 7, 2012)

Observation 1

Failure to assure that reserve samples came from the same samples used in the specific bioequivalence study identified by the agency, and failure to adequately identify said samples to assure positive identification. Specifically in regards to the multi-center study Protocol ZPS-411, the Dunedin site housed reserve samples for both for the Dunedin site and the Waikato site. The samples returned from the Waikato site were commingled with the Dunedin site. Upon collection of the reserve samples by the agency, there was no positive identification on the samples that allowed the agency to identify which samples were from the Dunedin site and which samples were from the Waikato site.

Zenith acknowledged the observation and stated that this was the first multi-site study they had conducted and they did not understand the regulation for retention of reserve samples during such multi-site studies. The samples returned from the Waikato clinical site were hence comingled and not stored separately. However, Zenith pointed out that the sponsor had no role in selection of the sequence of investigational products administered to each patient on the study.

As a preventive action, Zenith has assured that during conduct of all future multi-site studies, each Principal Investigator will be responsible for drug accountability and traceability. Zenith also assures that adequate amounts of drug products would be provided to each of the study sites who will independently dispense the drug products and retain adequate amount of appropriately labeled reserve samples. If the reserve samples from a multi-center study were to be stored at Zenith, they would be adequately identified upon receipt.

DBGLPC's Assessment of Data Integrity: Although the reserve samples coming from the two clinical sites Zenith and Waikato were comingled, the study was not blinded and the reference and test formulations were different in appearance (suspension vs solid oral dosage form). The sponsor had sent the investigational products (reference and test drugs) for the study as one shipment to Zenith.

The reference and test drugs from the same shipment were used at both clinical sites during the study. The subject case report forms clearly identified the dosage forms given to individual subjects. Hence, even though the reserve samples were comingled, they can be identified as coming from the same source used during the clinical study. The

DBGLPC reviewer is of the opinion that observation 1 should not have a significant impact on the study outcome.

Observation 2

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

A. Source data does not match the data submitted to the agency. For Protocol ZPS-411, the C-SSRS questionnaires for dosed Subject 9 submitted to the agency did not match the source information available at the site, specifically the Suicidal Behavior data.

In their response, Zenith acknowledged that one of their staff members had made additions to the C-SSRS questionnaires for subject 9 where a "0" was added to the "total number of attempts" column for suicidal behavior after the document was scanned for submission. Zenith believes that it was unnecessary as the check box was already selected for no suicide attempts for this subject and this change did not alter the data submitted to the agency. They acknowledged that they are unable to identify the reason behind the change as the staff member is no longer employed at Zenith. As corrective action, the copy was amended and forwarded to the sponsor. To prevent future occurrence, Zenith has initiated a new SOP which detailed the best practices of handling source documents. All staff handling/completing source documents were to be trained on this SOP by June 27, 2012.

DBGLPC's Assessment of Data Integrity: Zenith did not follow best documentation practices and they are of concern as they can raise general questions on the reliability and integrity of the study data. However, based on the response, this reviewer
thinks that observation 2a, by itself, does not affect the study
outcome.

Clinical site 2:

Puna-A-Tarle, Puna Maatai Puawai, Waikato Hospital, Hamilton, New Zealand (Inspection Date: May 23, 2012 by CG, Response to FDA-483: June 10, 2012)

Page 5 – NDA 203-479, Clozapine oral suspension, 50 mg/ml

Observation 1

Failure to retain reserve samples specific to an in vivo bioequivalence study.
Specifically in regards to the multi-center study Protocol ZPS-
411, you have not retained reserve samples for this study. All study drugs, both used and unused, were returned to the Dunedin site, which was not apart of the study protocol.

Waikato site acknowledged the observation and stated that this study was conducted under the guidance and supervision of Staff from Zenith Technology Corp. Ltd. and the Waikato investigator, subcontracted by (b) (4) was unaware of the requirement for retention of reserve samples as this was not stipulated in the Protocol for this study. However, they promised to work with Zenith for clear stipulation regarding retention of reserve samples in study protocols during future studies to prevent similar occurrences.

DBGLPC's Assessment of Data Integrity: Waikato clinical site did not maintain the reserve samples as required by regulation and instead sent them back to Zenith. However, as Zenith was not
the sponsor, manufacturer or packager, the integrity of the reserve samples was not compromised. Furthermore, the reference and test formulations used at Waikato and Zenith clinical sites came from a single shipment and were

different in appearance (Suspension vs solid oral dosage form). Zenith staff
transported the study drugs to the Waikato site without involvement of the sponsor. Also, the subject case report forms clearly identified the dosage forms given to each subject. In the opinion of this reviewer, observation 2 is unlikely to affect study outcome as the subject treatments could be confirmed from other source documents.

Observation 2

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically in regards to Protocol ZPS-411,

A. Source data from the Patient Study Record and Adverse Reactions form does not match the data submitted to the agency. i. Dosed Subject 25 - Days 1, 2, and 5
ii. Dosed Subject 26 -Day 4
iii.Dosed Subject 29 - All Days

In their response, Waikato site stated that all source data were scanned by Zenith for submission to the sponsor. The response included the original pages of the patient study records which matched with the records submitted to the agency. No
alterations were revealed in factual information. The response also stated that the patient study records for subjects 25, 26 and 29 were transcribed for clarity, however no factual information was changed.

As corrective and preventive action, Zenith has initiated a new SOP which details the best practices of handling source documents. All staff handling/completing source documents were to be trained on this SOP by June 27, 2012.

DBGLPC's Assessment of Data Integrity: In the opinion of the DBGLPC reviewer, the factual information did not change between the original and the transcribed document as evident from the original documents provided for comparison by Zenith, and therefore, the above observation should not have a significant impact on the outcome of the overall study data.

B. Post study safety labs were outside the date range specified in ProtocolZPS-411 for dosed Subjects 3, 19-25 and 27-30.

In their response, the Waikato site stated that many subjects did not have reliable transportation and did not wish to return for the post study safety labs. Hence, the post study safety samples were collected immediately after the final study sample was collected on day 23. Due to an oversight, collection of these samples at the earlier date was not recorded as a protocol deviation. As a corrective action, the Zenith promised to generate a study record form (SRF) to record all protocol deviations during the study and notify the sponsor. These corrective actions were to be finalized by July 6, 2012.

DBGLPC's Assessment of Data Integrity: The above observations should not have a significant impact on the outcome of the overall study data.

Analytical site:
Zenith Technology Corporation Ltd., Dunedin, New Zealand (Inspection Dates: May 14-25, 2012 by CG and AD, Response to FDA-483: June 15, 2012)

Page 7 – NDA 203-479, Clozapine oral suspension, 50 mg/ml

Observation 1
Failure to accurately report the bench top stability experiment conducted during pre-study method validation.

Specifically, in the first experiment for evaluation of bench top stability for 2 and 4 hours for clozapine, data generated for 2 hours bench top stability failed to meet acceptance criteria. A second bench top stability experiment was conducted subsequently. Data for 4-hours bench top stability from the first experiment and data for 2-hours bench tap stability from the second experiment were reported together and there was no mention of the failed data in the method validation report.

In their response, Zenith acknowledged the observation and promised to report all data including failed data with reasons for failure in the validation report. In the response, they have also included the amended validation report including the data from the failed run. They

believe the 2 hour bench top stability experiment failed due to possible sample processing error.

DBGLPC's Assessment of Data Integrity: During the validation study, the 2-hour bench top stability experiment failed to meet acceptance criteria (+/-15% of nominal concentration). However, during analysis of subject samples, clozapine QCs processed identically as subject samples were compared to freshly-prepared calibrators. This allows for evaluation of QC stability used within the run to freshly prepared calibration standards which had not undergone any degradation due to freeze-thaw (or storage at room temperature for which bench top stability needs to be demonstrated). As such, if there were stability concerns under the conditions used for subject sample processing, this would have been reflected in the precision and accuracy data of QC samples included in each run, and the runs would have been rejected. Additionally, the inspected lab had demonstrated
bench-top stability up to four hours, and the study passed. It is highly improbable that stability of the same samples would fail at two hours, then pass at four. Therefore, it appears reasonable that the initial 2-hour stability study failed due to sample processing error, as the response from Zenith suggested.

This reviewer is of the opinion that observation 1 should not have a significant impact on the study data.

Conclusions:

Following review and evaluation of the Form FDA-483 observations and responses from the inspected sites, this DBGLPC reviewer is of the opinion that the clinical and analytical data generated for studies C11-005-LBB (ZPS 411) were not affected by the cited deficiencies.

The reviewer recommends that the data for clinical and analytical portion of study C11-005-LBB (ZPS 411) be accepted for further agency review.

Arindam Dasgupta Ph.D.
Bioequivalence Branch, DBGLPC,
OSI

Final Classification:

VAI: Clinical Site #1 and Analytical
Zenith Technology Corporation Ltd., Dunedin, New Zealand
FEI: 3006135653

VAI: Clinical Site #2
Waikato Hospital, Hamilton,
FEI: 3004771398

4. OCP Comments-OSI Report

The report by the Office of Scientific Investigations points to several areas of concern related to sample retention, sample storage, and accuracy of case histories. None of these raise concern related to the integrity of the data submitted to the NDA. Therefore OCP finds the data submitted by Douglas Pharmaceuticals America to support NDA203-479 to be acceptable to OCP.

5.0 Detailed Study Information

5.1 Pharmacokinetics- Multiple Dose BE Study

Report # (ZPS-411) NDA 20347	**Study Period**: May-August 2011	EDR Link \\cdsesub1\EVSPROD\NDA203479\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\c11-005-lbb\clinical-study-report.pdf
Title	Multiple-dose, multi-centre, randomised, bioequivalence study of clozapine in multiples of 100 mg as 50 mg/ml Clozapine suspension (Douglas, America) in a two way crossover comparison with multiples of 100 mg as Clozaril® 100 mg tablet (Novartis, USA) in stable patients under fasting and fed conditions and at steady state.	
Study Design: A multi-centre, multiple-dose, randomised, two-treatment, two-period, two-sequence crossover steady state bioequivalence study, performed under fasting and fed conditions. On Day 11 of each study period, after fasting for at least 7.5 hours and within 5-minutes of consuming a USFDA standardised high-fat meal over a 30-minute period, patients were administered a multiple dose of either the Test or Reference formulation as determined by the Randomisation Scheme. Patients were confined to one of the three clinical sites from at least 10 hours prior to drug administration on days 10 and 21, until after the 48-hour post-dose blood draw on days 12 and 23 for each group. There was no washout period between the two treatment periods.		
Demographics: Psychotic Illness in good health		
Doses by Group: Test (T) (Treatment II): Clozapine 50 mg/ml suspension, Douglas, America		

Batch No.: 7805.005A, Manufactured: 20 Sep 2010
Reference (R) (Treatment I): Clozaril® 100 mg tablets, Novartis, USA
Batch No.: F0133, Expiry: Dec 2012

Doses were administered daily in the evening, under fasting and fed conditions and at steady state, to assess the biostatistical equivalence of the pharmacokinetic parameters for the two formulations.
On Day 10 of each study period, patients fasted for at least 8 hours prior to being administered a multiple dose of either the Test or Reference formulation as determined by the Randomization Scheme. On Day 11 of each study period, after fasting for at least 7.5 hours and within 5-minutes of consuming a USFDA standardised high-fat meal over a 30-minute period, patients were administered a multiple dose of either the Test or Reference formulation as determined by the Randomization Scheme

The treatments were administered orally starting at approximately 20:00 (0.0 hour).
There was no washout between study periods.
The patient dosing regime based upon their stabilized 3 week dose is summarized below:

Patients	Dose	Sequence	Day 1 to 11	Day 12 to 22
D01-01	400 mg	T/R	CLO*	CZL*
D02-02	100 mg	T/R	CLO	CZL
W17-03	600 mg	R/T	CZL	CLO
D04-04	400 mg	T/R	CLO	CZL
D05-05	700 mg	T/R	CLO	CZL
D06-06	500 mg	R/T	CZL	CLO
D07-07	400 mg	R/T	CZL	CLO
D08-08	300 mg	T/R	CLO	CZL
D09-09	400 mg	T/R	CLO	CZL
D15-10	650 mg	R/T	CZL	CLO
D11-11	100 mg	R/T	CZL	CLO
D12-12	200 mg	T/R	CLO	CZL
D13-13	600 mg	R/T	CZL	CLO
D14-14	350 mg	R/T	CZL	CLO
D16-15	600 mg	T/R	CLO	CZL
D18-16	100 mg	T/R	CLO	CZL
D19-17	800 mg	R/T	CZL	CLO
D20-18	350 mg	T/R	CLO	CZL
W02-19	400 mg	T/R	CLO	CZL
W15-20	400 mg	R/T	CZL	CLO
W01-21	350 mg	R/T	CZL	CLO
W03-22	450 mg	T/R	CLO	CZL
W13-23	700 mg	T/R	CLO	CZL
W16-24	700 mg	R/T	CZL	CLO
W07-25	350 mg	R/T	CZL	CLO
W14-26	500 mg	T/R	CLO	CZL
W05-27	500 mg	R/T	CZL	CLO
W12-28	400 mg	T/R	CLO	CZL
W04-29	400 mg	R/T	CZL	CLO
W09-30	100 mg	R/T	CZL	CLO

* CLO (T) (II) Clozapine 50 mg/ml suspension (Douglas, America, Batch No 7805.005A)

* CZL (R) (I) Clozaril® 100 mg tablets (Novartis, USA, Batch No F0133)

PK Sampling Times: Blood samples were drawn prior to dose administration on Study Days 1, 7, 8, 9 and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 20 and 24 hours after drug administration on Study Days 10, 11 of each study period.

Analytical Method:

Type	LS/MS/MS	Range 15-384 ng/ml	
The performance of the analytical method is acceptable.		☒ Yes ☐ No	

Study Population : Male and non-pregnant female patients with treated psychotic illnesses, in general good health, who are stabilised (for at least 3 months) on multiples of 100 mg clozapine once daily (evening),

Randomized/Completed/ Discontinued Due to AE	30/30
Age [Mean (range)]	38(24-57)
Male/Female	25/5
Race (European /Maori//other)	16/11/3

Results

- Pharmacokinetics Parameters Per Dose Group, Mean (%CV)

See attached Tables.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Comments

1. The BE study is acceptable. The clozapine 50 mg/ml suspension is bioequivalent to the Clozaril® 100 mg tablet. For AUC and Cmax, the food effect for 50 mg/ml suspension is similar to Clozaril ® tablets.
2. The fed study Tmax values for the tablet occur at 5 h whereas under fasting conditions they occur at 2 h. However since the drug is given at steady-state this would not impact clinical response.

Table 1. Fasted results

Summary Results:

Fasting Pharmacokinetic Results:

Pharmacokinetic Parameters	Clozapine 50 mg/ml suspension (II) Batch: 7805.005A, Douglas, America (n=30) (mean ± S.D) (Range)	Clozaril® 100 mg tablets (I) Batch: F0133, Novartis, USA (n=30) (mean ± S.D) (Range)
AUC_{0-t} (ng.hr/ml)	3223.09±1452.61 (721.51-8329.98)	3284.70±1355.04 (978.22-7602.87)
Cmax (ng/ml)	275.01±104.90 (104.59-722.84)	275.09±98.69 (127.92-654.14)
Cmin (ng/ml)	74.70±38.73 (10.73-197.73)	74.64±40.79 (9.10-210.56)
DF (%)	163.01±51.22 (85.70-312.22)	157.73±45.98 (92.68-291.50)
Tmax (hr)	2.18±0.85 (1.00-3.52)	2.53±1.25 (1.00-6.00)

	Clozapine 50 mg/ml suspension (II) vs Clozaril® 100 mg tablet (I)			
	Anova	Mean ratio %	Geometric mean ratio %	90% confidence interval
$Log_{10}(AUC_{0-t})$	0.161	99.55	-	(0.924,1.007)*
Log_{10}(Cmax)	0.870	99.91	-	(0.946,1.047)*
Log_{10}(Cmin)	0.559	100.29	-	(0.978,1.047)
AUC_{0-t}	0.429	98.12	96.44	(0.942,1.021)
Cmax	0.993	99.97	99.51	(0.947,1.052)
Cmin	0.968	100.09	101.20	(0.964,1.037)
DF	0.300	103.35	-	(0.980,1.087)
Tmax	0.139	86.23	-	(0.709,1.016)
Tmax[a]	-	-	-	(0.764,1.002)

* Criteria used to assess Bioequivalence i.e. 90% CI between 0.80 and 1.25 for AUC_{0-t} and Cmax

[a] Nonparametric Analysis

* AUC0-t is actually AUC0-tau

Table 2. Fed results

Summary Results:

Fed Pharmacokinetic Results:

Pharmacokinetic Parameters	Clozapine 50 mg/ml suspension (II) Batch: 7805.005A, Douglas, America (n=30) (mean ± S.D) (Range)	Clozaril® 100 mg tablets (I) Batch: F0133, Novartis, USA (n=30) (mean ± S.D) (Range)
AUC_{0-t} (ng.hr/ml)	3059.15±1280.21 (702.48-7540.92)	3090.08±1214.51 (967.96-6970.06)
Cmax (ng/ml)	220.16±82.73 (82.92-525.20)	220.48±74.49 (107.39-466.41)
Cmin (ng/ml)	72.58±40.41 (10.73-219.46)	71.81±38.54 (9.10-193.64)
DF (%)	122.82±36.76 (64.79-246.64)	122.46±36.80 (66.34-243.70)
Tmax (hr)	3.12±2.29 (1.00-12.00)	4.94±2.84 (1.00-14.00)

	Clozapine 50 mg/ml suspension (II) vs Clozaril® 100 mg tablet (I)			
	Anova	Mean ratio %	Geometric mean ratio %	90% confidence interval
$Log_{10}(AUC_{0-t})$	0.321	99.68	-	(0.934,1.018)*
Log_{10}(Cmax)	0.604	99.72	-	(0.937,1.035)*
Log_{10}(Cmin)	0.366	100.34	-	(0.988,1.041)
AUC_{0-t}	0.671	99.00	97.50	(0.950,1.030)
Cmax	0.959	99.86	98.49	(0.951,1.046)
Cmin	0.556	101.08	101.40	(0.980,1.042)
DF	0.922	100.29	-	(0.954,1.052)
Tmax	0.004	63.17	-	(0.434,0.830)
Tmax[a]	-	-	-	(0.478,0.756)

* Criteria used to assess Bioequivalence i.e. 90% CI between 0.80 and 1.25 for AUC_{0-t} and Cmax

[a] Nonparametric Analysis

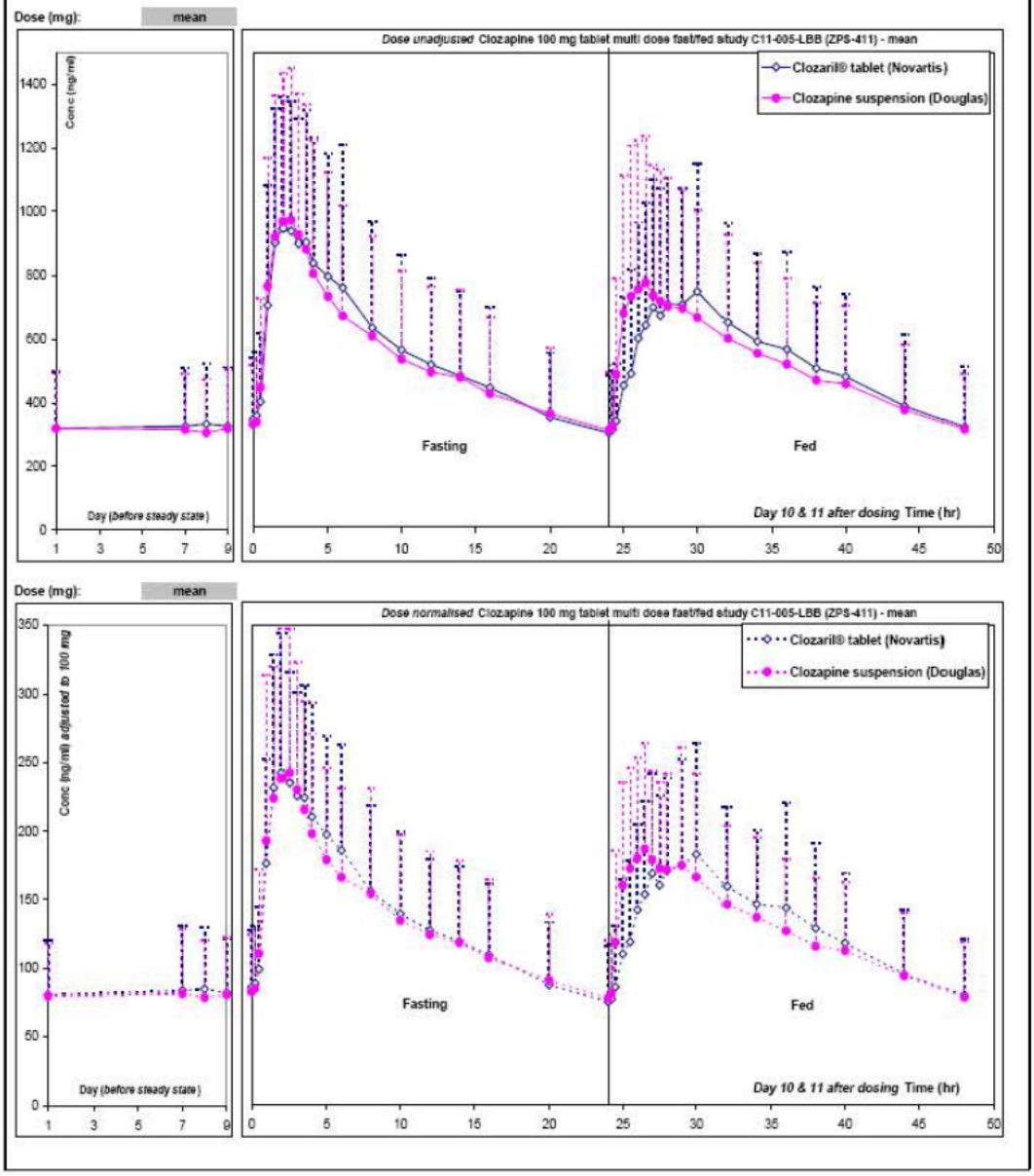
AUC0-t is actually AUC0-tau

Figure 1. Mean graphs for fasted and fed administration at steady-state.

Summary Results:

Pharmacokinetic Profiles:

Mean concentration (ng/ml) versus Time (hrs) for clozapine following oral administration of multiples of 100 mg Clozapine suspension (Douglas, America) (Test) and multiples of 100 mg Clozaril® tablet (Novartis, USA) (Reference) under fasting and fed conditions at time zero and at steady state.



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/s/

ANDRE J JACKSON
08/07/2012

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08/07/2012